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Clinical Study

Safety, efficacy, and cost of intraoperative indocyanine green angiography compared to intraoperative catheter angiography in cerebral aneurysm surgery

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ABSTRACT

Intraoperative angiography in cerebrovascular neurosurgery can drive the repositioning or addition of aneurysm clips. Our institution has switched from a strategy of intraoperative digital subtraction angiography (DSA) universally, to a strategy of indocyanine green (ICG) videoangiography with DSA on an as-needed basis. We retrospectively evaluated whether the rates of perioperative stroke, unexpected postoperative aneurysm residual, or parent vessel stenosis differed in 100 patients from each era (2002, "DSA era"; 2007, "ICG era"). The clip repositioning rate for neck residual or parent vessel stenosis did not differ significantly between the two eras. There were no differences in the rate of perioperative stroke or rate of false-negative studies. The per-patient cost of intraoperative imaging within the DSA era was significantly higher than in the ICG era. The replacement of routine intraoperative DSA with ICG videoangiography and selective intraoperative DSA in cerebrovascular aneurysm surgery is safe and effective.

1. Introduction

Residual aneurysm filling, parent vessel stenosis, and perforating artery compromise have complicated open clipping of aneurysms since the origin of cerebrovascular neurosurgery. In the last decade, our institution and others have advocated the routine or selective use of intraoperative digital subtraction angiography (DSA) to assess aneurysm residual and vessel patency [1–7]. Some neurosurgeons have advocated selective intraoperative DSA use, such as in large or complex aneurysms only, and cited that routine DSA is not necessarily cost-effective [4]. However, our group has previously published a study of routine DSA in all aneurysm clip patients, and found that surgeons could not always predict preoperatively when intraoperative DSA would be useful, suggesting more routine use [5].

Indocyanine green (ICG) is a near-infrared (NIR) fluorescent compound utilized since the 1950s in humans for liver diagnostics and subsequently approved by the US Food and Drug Administration for ophthalmologic angiography in the 1970s. ICG is excreted unchanged via the hepatic system and the incidence of major or minor complications associated with systemic exposure is minimal. The dye is injected intravenously, is quickly plasma-protein bound, and reaches the cerebral vasculature within 30 seconds. The first report of indocyanine green angiography (ICGA) in cerebrovascular surgery utilized a separate NIR light source and NIR-sensitive video camera, but soon afterwards the technology for both the NIR light source and recording was integrated into the surgical microscope [8,9]. This allows for the real-time visualization of vessel flow and aneurysm filling within the surgical field in both arterial and venous phases. In the last decade, our group and others have successfully utilized ICGA in surgery for elective and ruptured cerebral aneurysms, intracranial–extracranial bypass, and cerebral arteriovenous malformations [9–24]. ICGA has similar rates of clip repositioning and parent vessel stenosis when compared head-to-head with either intraoperative or postoperative DSA [9,23,25]. Published studies have focused on the technical sensitivity and specificity of ICGA when compared to a "gold standard" of intraoperative or postoperative DSA in patients receiving both imaging modalities. This literature has established ICGA as a viable alternative to intraoperative DSA, but these studies are focused on technical comparisons of the imaging modalities. However, no study to our knowledge has compared patient outcomes following the replacement of intraoperative DSA with routine ICGA in a clinical practice. While ICG is a more rapid and convenient form of angiography in clinical practice, its value would be much less if its use was not associated with similar or better outcomes. Our institution now routinely employs ICGA during

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aneurysm surgery with the selective use of intraoperative DSA and micro-Doppler techniques; this practice evolved over the era of the Barrow Ruptured Aneurysm Trial (BRAT) [26,27]. Our clinical experience represents a natural comparison of the two diagnostic methods via retrospective review of two "eras": the year prior to BRAT (2002), in which the intent was for all aneurysm clipping patients to receive intraoperative DSA, and the year after BRAT (2007), in which the primary intraoperative angiographic modality for aneurysm clipping patients was to receive ICGA. We assembled the present study not to compare the previously published intraoperative utility of ICGA *versus* intraoperative DSA, but rather to assess if a paradigm shift away from routine intraoperative DSA to routine ICGA with selective intraoperative DSA would result in similar patient outcomes, such as stroke and return to the operating room for unexpected postoperative imaging findings.

2. Methods

2.1. Study population

We retrospectively identified all aneurysms treated via open microsurgical clipping in the years 2002 ("DSA era") and 2007 ("ICG era") at the Barrow Neurological Institute, AZ, USA using a departmental registry. The first 100 patients in each year with available inpatient and outpatient records were identified and analyzed. This study was approved by the St. Joseph's Hospital and Medical Center Institutional Review Board for human research.

2.2. Data collection

Hospital and clinical records were reviewed, as were pre and postoperative imaging studies. Each patient was treated by an experienced cerebrovascular neurosurgeon (R.F.S., P.N., or J.M.Z.). Intraoperative DSA was performed by an endovascular neurosurgeon or a diagnostic neuroradiologist. Patient characteristics identified included age at surgery, sex, aneurysm size and location, the form of intraoperative imaging used, and pre and postoperative neurological deficits. Each patient was assessed for perioperative stroke, defined here as a new permanent or transient neurological deficit within 72 hours of surgery with an appropriate imaging correlate on MRI or CT scan. Technical difficulties with either imaging modality were noted, as were residual aneurysm filling and parent vessel occlusion on independent postoperative imaging such as follow-up DSA, computed tomography angiography (CTA), or magnetic resonance angiography (MRA).

2.3. Statistical analysis

Univariate analysis to compare categorical variables was performed using Fisher's exact test with a probability value of <0.05 considered statistically significant. Univariate analysis to compare continuous variables was performed using Student's *t*-test with a probability value of <0.05 considered statistically significant. All analyses were conducted using GraphPad QuickCalcs (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

3.1. Patient demographics

We identified the first 100 consecutive patients undergoing 100 craniotomies for the treatment of 119 aneurysms in the year 2002 ("DSA era," Table 1), and the first 100 consecutive patients undergoing 100 craniotomies for the treatment of 122 aneurysms in the year 2007 ("ICG era," Table 1). The average age between patients in each era did not differ significantly (52.2 years in DSA era, 54.0 years in ICG era, p = not significant [NS]). A female predominance was seen in both study periods. More patients presented with aneurysm rupture and subarachnoid hemorrhage (aSAH) in the DSA era than in the ICG era (49% *versus* 30%, $p = 0.008$, Fisher's exact test). Furthermore, more middle cerebral artery (MCA) aneurysms and fewer posterior communicating artery (PCoA) aneurysms were treated in the ICG era than DSA era (30% *versus* 11% and 3% *versus* 18%, respectively, $p < 0.05$, Fisher's exact test). Regardless of the modality used intraoperatively, all patients at our institution underwent CTA, MRA, and/or DSA postoperatively within 24 hours of surgery as a control.

Table 1
Patient demographics

	DSA era	ICG era
Patients	100	100
Treated aneurysms	119	122
Mean age, years	52.2	54.0
Sex, M:F	26:74	34:66
Presentation		
Elective	46*	64*
Acute SAH	49*	30*
Remote SAH	5	6
Location, n (%)		
Anterior circulation	97 (82%)	108 (89%)
ACoA	19 (16%)	30 (25%)
ACA	9 (8%)	2 (2%)
ICA	24 (20%)	20 (16%)
MCA	13 (11%)*	36 (30%)*
OphthA	10 (8%)	16 (13%)
PCoA	22 (18%)*	4 (3%)*
Posterior circulation	22 (18%)	14 (11%)
AICA	3 (3%)	0 (0%)
BasilarA	8 (7%)	6 (5%)
PCA	2 (2%)	0 (0%)
PICA	7 (6%)	5 (4%)
SCA	2 (2%)	3 (2%)
Intraop DSA	81%*	13%*
Intraop ICG	0%*	79%*
Periop stroke	4%	3%
Clip repositioning	6%	4%
False-neg rate	1%	1%
Routine postop DSA	12%	8%

ACA = anterior cerebral artery, ACoA = anterior communicating artery, AICA = anterior inferior cerebellar artery, BasilarA = basilar artery, DSA = digital subtraction angiography, F = female, False-neg = false-negative study, ICA = internal carotid artery, ICG = indocyanine green, Intraop = intraoperative, M = male, MCA = middle cerebral artery, OphthA = ophthalmic artery, PCA = posterior cerebral artery, PCoA = posterior communicating artery, Periop = perioperative (within 72 hrs), PICA = posterior inferior cerebellar artery, postop = postoperative, SAH = subarachnoid hemorrhage, SCA = superior cerebellar artery.
* $p < 0.05$ comparing DSA era to ICG era.

3.2. Utilization of intraoperative modalities

In the DSA era, 81% of patients underwent intraoperative DSA; none underwent ICGA as it had not yet been introduced at our institution. In the ICG era, 79% of patients underwent ICGA, and 13% of patients underwent intraoperative DSA either in conjunction with (2%) or as a substitution of (11%) ICG. Patients who underwent intraoperative DSA within the ICG era did not differ from patients who underwent ICGA alone in any variable examined (Table 2). In one patient treated with ICGA, the parent vessel could not be adequately visualized and so intraoperative DSA was utilized. Otherwise, there were no cases of intraoperative technical failure using either technique. No patient suffered an allergic reaction to either injected iodinated contrast or ICG. No pseudoaneurysms or

Table 2
Comparison of patients within ICG era

	ICG only	DSA only or DSA + ICG
Patients	78	13
Treated aneurysms	94	16
Mean age, years	55.6	52.6
Acute SAH	30 (38%)	3 (23%)
Location, n (%)		
Anterior circulation	83 (88%)	16 (100%)
ACoA	23 (24%)	5 (31%)
ACA	2 (2%)	0 (0%)
ICA	15 (16%)	2 (12.5%)
MCA	28 (30%)	7 (44%)
OphthA	1 (1%)	1 (6%)
PCoA	14 (15%)	1 (6%)
Posterior circulation	11 (12%)	0 (0%)
AICA	0 (0%)	0 (0%)
BasilarA	4 (4%)	0 (0%)
PCA	0 (0%)	0 (0%)
PICA	5 (5%)	0 (0%)
SCA	2 (2%)	0 (0%)
Periop stroke, n (%)	3 (4%)	0 (0%)
Clip repositioning, n (%)	3 (4%)	1 (8%)

ACA = anterior cerebral artery, ACoA = anterior communicating artery, AICA = anterior inferior cerebellar artery, BasilarA = basilar artery, DSA = digital subtraction angiography, F = female, ICA = internal carotid artery, ICG = indocyanine green, M = male, MCA = middle cerebral artery, OphthA = ophthalmic artery, PCA = posterior cerebral artery, PCoA = posterior communicating artery, Periop = perioperative (within 72 hours), PICA = posterior inferior cerebellar artery, SAH = subarachnoid hemorrhage, SCA = superior cerebellar artery.

retroperitoneal hematomas were seen in patients undergoing intraoperative DSA in either era.

3.3. Clinical utility and stroke outcomes

Both modalities altered surgical practice in the form of providing information that led to the repositioning or addition of aneurysm clips due to findings of aneurysm filling or parent vessel stenosis in select patients. In the DSA era, intraoperative angiography demonstrated residual aneurysm filling in four patients and vessel stenosis in two patients for a total of six clip adjustments (6%). In the ICG era, two patients demonstrated intraoperative residual aneurysm filling requiring clip repositioning or additional clips, and two patients had vessel stenosis for a total repositioning rate of 4% (p = NS when compared to DSA era). Of these four patients, one required both DSA and ICGA to properly assess distal vessel stenosis in a complex anterior communicating artery (ACoA); the other three patients underwent ICGA only prior to clip revision.

One patient in the DSA era undergoing elective basilar tip aneurysm clipping, who received intraoperative DSA, had a small unexpected area of aneurysm filling as seen on postoperative DSA after the patient suffered aSAH on postoperative day 2 (false-negative rate, 1%). This was managed conservatively, and follow-up angiography demonstrated total aneurysm obliteration. One patient in the ICG era undergoing elective MCA bifurcation aneurysm clipping, who received ICGA only, had unexpected parent vessel stenosis as observed on postoperative day 3 DSA

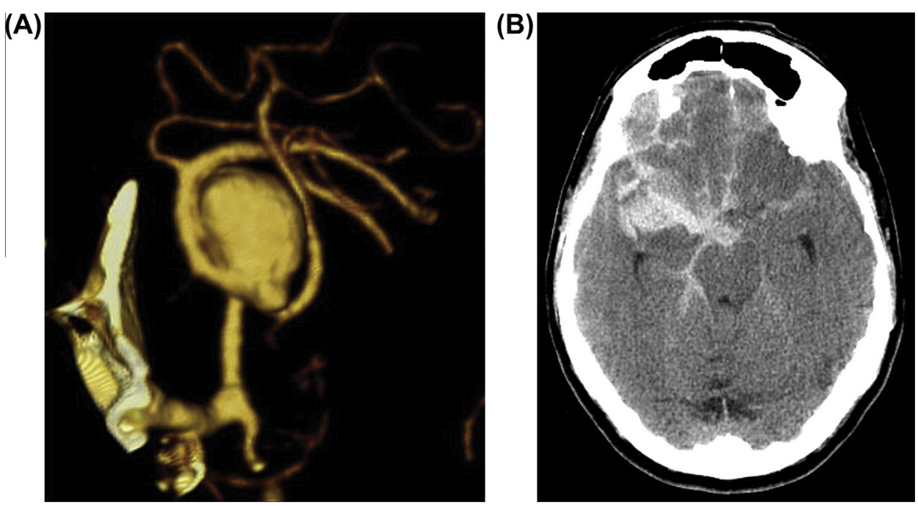

Fig. 1. (A) Computed tomography angiography three-dimensional reconstruction demonstrates a right middle cerebral artery aneurysm responsible for (B) a Fisher grade III subarachnoid hemorrhage with a right Sylvian fissure clot seen on axial CT scan. *Used with permission from Barrow Neurological Institute.*

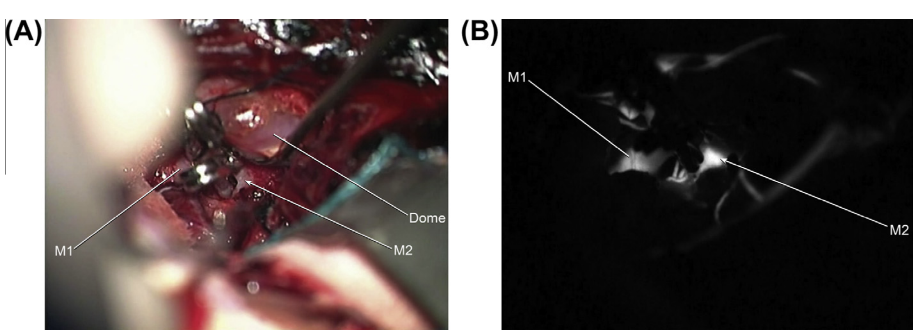

Fig. 2. During surgery, the smaller superior branch (A, arrow) showed good filling distally on indocyanine green videoangiography (B, arrow) but could not be completely visualized. *Used with permission from Barrow Neurological Institute.*

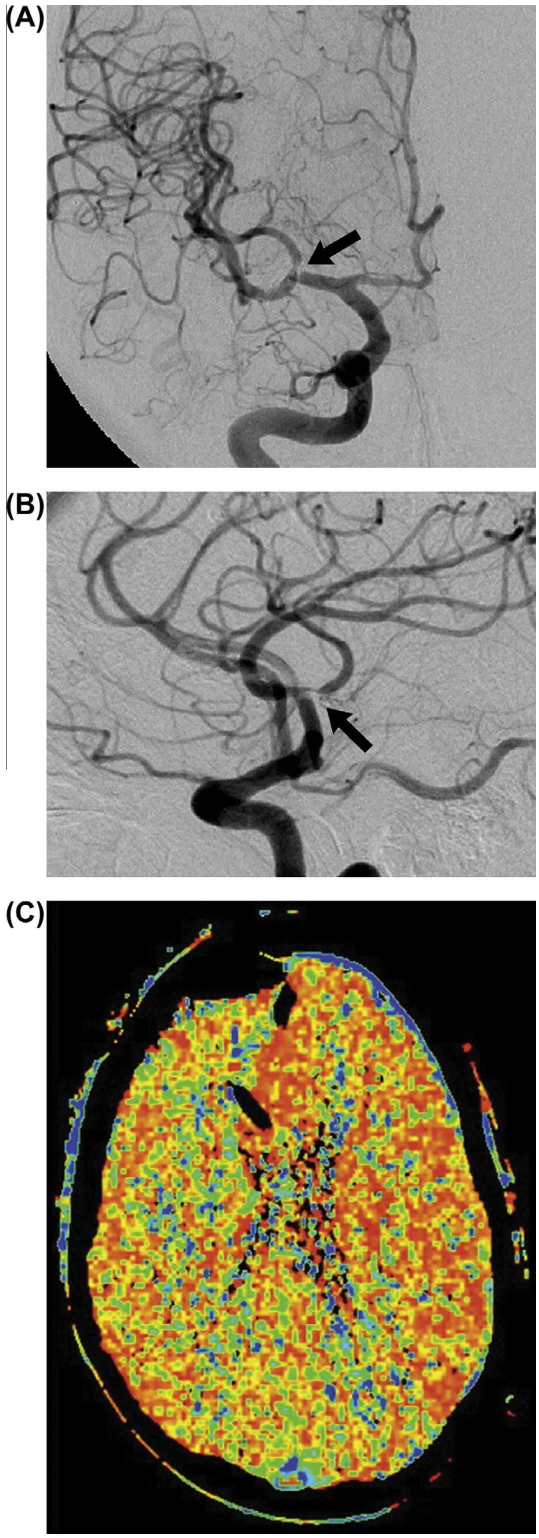

Fig. 3. (A) Postoperative anteroposterior and (B) lateral right internal carotid artery angiography demonstrated severe stenosis of the smaller branch (arrows). The patient subsequently developed a left pronator drift and axial CT perfusion scan (C) showed cerebral hypoperfusion on the right. *Used with permission from Barrow Neurological Institute*.

(false-negative rate, 1%). The patient returned to the operating room for clip repositioning, with no neurological sequeleae (Fig. 1–4).

In the DSA era, perioperative strokes occurred in four patients (4%, Table 2). These patients suffered an ipsilateral caudate head infarct after internal carotid artery aneurysm clipping with transient dysarthria (Patient 1), an ipsilateral MCA–posterior cerebral artery watershed infarct after ophthalmic artery aneurysm clipping with no significant sequelae (Patient 2), a cerebellar posterior inferior cerebellar artery (PICA) infarct due to intraoperative vessel avulsion and sacrifice during PICA aneurysm clipping with postoperative respiratory failure requiring tracheostomy (Patient 3), and a cerebellar PICA infarct due to proximal vessel stenosis after PICA aneurysm clipping with no significant sequelae (Patient 4). All patients except Patient 3 received intraoperative DSA and Patient 4 had intraoperative clip repositioning but persistent vessel stenosis. In the ICG era, there were three (3%) perioperative strokes (Table 3). These included a brainstem perforator infarct after basilar artery aneurysm clipping with a permanent hemiparesis (Patient 5), an ipsilateral internal capsule infarct after MCA aneurysm clipping with transient hemiparesis (Patient 6), and an ipsilateral internal capsule infarct after clipping of ACoA and PCoA aneurysms with transient hemiparesis (Patient 7). All three ICG era patients received ICGA, and Patient 6 had intraoperative clip repositioning. There was no statistically significant difference in the incidence of perioperative stroke between the DSA and ICG era patients (p = NS). There was no reduction in the utilization of immediate postoperative DSA (within 24 hours of surgery) in the routine intraoperative DSA era when compared to the ICG era (12% *versus* 8%, respectively, p = NS).

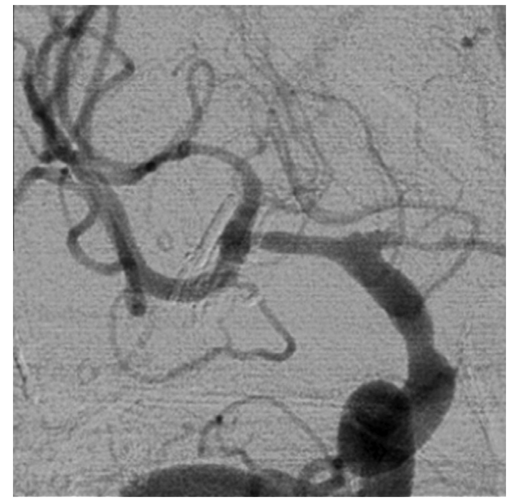

Fig. 4. Intraoperative anteroposterior angiogram after the clip was revised at a second craniotomy shows no residual stenosis. The patient did well clinically and made a modified Rankin Scale score 1 recovery. *Used with permission from Barrow Neurological Institute*.

3.4. Cost

Both intraoperative DSA and ICGA have significant buy-in cost related to equipment purchases, such as fluoroscopy machines, technicians, and/or NIR equipped surgical microscopes. These costs vary widely between institutions based on established equipment, and we did not seek to quantify these initial costs.

We analyzed two factors in relation to the cost of each intraoperative imaging modality. First was the length of time required for acquiring images; at our institution, an ICGA "run" takes under 3 minutes, while intraoperative DSA takes approximately 15 to 20 minutes. This translates to an additional cost at our institution, based on billing per 15 minutes of operating room time, of $USD2290 for DSA. Secondly, we analyzed the patient charge for the procedure itself. At our institution, ICGA carries no additional patient charge beyond the minor cost of the intravenous dye itself.

Table 3
Details of perioperative strokes by era

Patient	Age, years	Aneurysm location(s)	SAH/Elective	Event	Sequelae	Modality used	Intraop clip reposition?
DSA era							
1	47	ICA ($\times$ 3)	Elective	Caudate infarct	Transient dysarthria	DSA	No
2	41	OphthA	Elective	MCA/PCA watershed infarct	None	DSA	No
3	68	PICA	SAH	Cerebellar infarct	Tracheostomy	None	No
4	48	PICA	SAH	Cerebellar infarct	None	DSA	Yes
ICG era							
5	50	BasilarA	Elective	Perforator infarct	Hemiparesis	ICG	No
6	65	MCA	Elective	Internal capsule infarct	Transient hemiparesis	ICG	Yes
7	56	ACoA, PCoA	SAH	Internal capsule infarct	Transient hemiparesis	ICG	No

ACoA = anterior communicating artery, BasilarA = basilar artery, DSA = digital subtraction angiography, ICA = internal carotid artery, ICG = indocyanine green, Intra-op = intraoperative, MCA = middle cerebral artery, OphthA = ophthalmic artery, PCA = posterior cerebral artery, PCoA = posterior communicating artery, PICA = posterior inferior cerebellar artery, SAH = subarachnoid hemorrhage.

In contrast, DSA acquisition and interpretation is currently billed to patients at a cost of $USD14,522 for a single carotid or vertebral artery injection, as well as the relatively minor cost of disposable equipment. In the DSA era (81% DSA utilization), these two charges lead to an average cost of intraoperative angiography of $USD13,617 per patient. In comparison, using the same charges, the cost per patient of intraoperative angiography in the ICG era (13% DSA utilization) was $USD2186.

4. Discussion

ICGA has over the last decade become an established method of assessing intraluminal flow in cerebrovascular neurosurgery. Compared to intraoperative DSA, advantages of ICGA include the speed of image acquisition, the ability to manipulate the surgical field during the ICG study, and improved resolution to assess even small perforating arteries. This is the first study to our knowledge comparing the safety and efficacy of a clinical practice transition to routine ICGA compared to an era of routine intraoperative DSA. Both modalities had a utilization rate of approximately 80% within their respective eras. The rates of detecting residual aneurysm dome filling or parent vessel stenosis intraoperatively were similar: no statistically significant differences were observed between the ICGA and intraoperative DSA eras, although event rates were low in both eras. Both modality eras had one false-negative study each: an unexpected aneurysm remnant in the DSA era and an unexpected parent vessel stenosis in the ICG era. The incidence of perioperative stroke also did not differ between eras (3% for ICG and 4% for intraoperative DSA) and these values are within the range reported in other large surgical series [13,4]. Lastly, the routine use of ICGA compared to routine DSA led to a per-patient cost reduction of $USD11,431 based on billing for operating room time and catheter angiography itself. However, service charges can vary widely per institution and so this cost reduction may not be generalizable, especially outside the USA. Furthermore, the acquisition cost of ICG-enabled surgical microscopes was not included in our analysis and also will vary widely based on institution. A single stroke, or return to the operating room for repositioning, would drastically alter any cost analysis and we did not attempt to analyze this further.

Our study is limited by its retrospective nature and we acknowledge the inherent pitfalls of any such analysis. Multiple factors not analyzed may differ between the eras, such as additional operating room technological advances, the surgeons performing clipping, and individual surgeon experience. Additionally it is possible that clips were more often repositioned due to vessel stenosis or residual aneurysm filling than we have reported, but that some of these events were not recorded within the operative report. Nonetheless, the purpose of this study was to assess the overall outcomes achieved with each era, and not to compare specific intraoperative utility between modalities. We attempted to minimize the number of strokes that were actually due to cerebral vasospasm by only including deficits suffered within 72 hours of surgery. However, some patients with subarachnoid hemorrhage will present with vasospasm immediately postoperatively, and therefore the strokes reported here may include events not directly related to surgical compromise. Lastly, some patients (13%) underwent intraoperative DSA within the ICG era. Thus, a selection bias whereby simpler aneurysms were examined using ICGA alone, and more complex aneurysms examined with DSA, cannot be excluded. However, no clinical variable that we studied differed between patients in the ICG era who underwent ICGA alone or those who underwent DSA as well as or without ICGA including aneurysm location, acute subarachnoid hemorrhage presentation, and number of aneurysms clipped per patient was significant. Furthermore, ours was a “real-world” retrospective study examining the clinical safety of routine ICGA use compared to routine DSA use. Therefore, the selective use of intraoperative DSA when needed as determined by the surgeon within the ICG era does not invalidate our overall conclusion that ICGA is a safe first-line intraoperative modality; we do not mean to suggest that ICGA can replace DSA in all cases.

High-quality intraoperative DSA still has an important role in aneurysm surgery, despite a transition to routine ICGA. Technically, ICGA is limited by the field of view of the operative microscope, and at times this precludes its use to assess all relevant vessels if obscured by the aneurysm or clip. Similarly, patients with highly calcified vessels or complex, partially thrombosed aneurysms may still be better suited for intraoperative DSA. However, intraoperative DSA remains itself an imperfect modality with up to a reported 5–8% rate of unexpected vessel stenosis or aneurysm filling compared to the “gold standard” of postoperative DSA [28]. Our experience is that postoperative imaging, either CTA or DSA, is required to fully assess the vasculature even after intraoperative DSA. As such, we found that the use of intraoperative DSA does not spare the patient additional postoperative imaging compared to ICGA. At our institution patients routinely undergo postoperative CTA or MRA with selective use of postoperative DSA, regardless of the utilized intraoperative modality. A combination of ICGA, intraoperative DSA, and/or micro-Doppler ultrasonography, postoperative vascular imaging, and the personal experience of a subspecialty-trained cerebrovascular neurosurgeon may be required for the most challenging aneurysms to avoid complications due to missed findings, and therefore to achieve the best possible patient outcomes.

5. Conclusions

An era utilizing routine ICGA with selective use of intraoperative DSA produced equally low rates of unexpected aneurysm filling, parent vessel compromise, and perioperative strokes when compared to an era utilizing routine intraoperative DSA. Intraoperative ICGA is a safe, effective, and cost-effective replacement to routine intraoperative diagnostic angiography. However, a role for postoperative imaging remains as no intraoperative modality can be considered as yet a gold standard.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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